REMARKS

This paper is submitted in response to the Office Action mailed August 21, 2003. Following this amendment, claims 50-99 are pending. Claims 94-99 have been added. Claims 56, 65-76, 80, 85 and 88-93 have been amended. Claims 56, 76, 90 and 93 have been amended to correct a typographical error. Support for amendments to claims 65-76, 80, 85 and 88-93 can be found in the specification at page 19, lines 19-24. Since support for the amendments and new claims can be found throughout the specification and claims as originally filed, there is no new matter added as a consequence of the amendments or new claims.

The Rejections under 35 U.S.C. § 112 Should Be Withdrawn

Claims 88-93 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in a way as to reasonably convey to one skilled in the art that the inventors, at the time of the invention, had possession of the claimed invention. The Examiner alleges that there is no support for the consensus sequences set forth in SEQ ID NOS: 13-18. The Examiner contends that SEQ ID NOS:1-11 provide support for claiming SEQ ID NOS:1-11 and not consensus sequences derived from these peptides.

Applicants respectfully disagree. What is conventional or well known to one of skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F2d at 1384, 231 USPQ at 94. It is adequate to "require only sufficient description to show one of skill in the art that the inventors possessed the claimed invention at the time of filing." *Union Oil Company of California v. Atlantic Richfield Company* 208 F.3d 989, at 997, 54 USPQ 2d 1227.

Consensus sequences are the average or most typical form of a sequence that is reproduced with minor variations in a group of related DNA, RNA or amino acid sequences,

showing the nucleotide or amino acid most often found at a particular position in the sequence. The presence of these consensus sequences, or motifs, also implies an important functional role shared by molecules possessing them. An alignment of amino acid sequences at the consensus regions of the sequences clearly demonstrates that the regions are homologous and are indeed consensus sequences. It is certainly within the knowledge of one of skill in the art to detect consensus sequences in an alignment of various sequences that exhibit common or substantially identical residues at the same positions, for example, substantially identical residues in terms of polarity, charge and hydrophobicity. Applicants assert that one of skill in the art would easily detect the consensus sequences of the present invention and recognize that the inventors were in possession of the claimed invention.

SEQ ID NOS: 13-18 are consensus amino acid sequences derived from the sequences set forth in SEQ ID NOS:1-11. It would be readily apparent to one of skill in the art that such sequences share the common motif as shown in Tables 1 and 4. For example in Table 1, the sequences listed at position 150-161 and position 150-161* reveal an array of consensus sequences. In fact, the sequences are arranged so that the shared positions that form the consensus sequence are aligned. The alignment clearly demonstrates shared sequences from which SEQ ID NOS: 16, 17 and 18 are derived. SEQ ID NOS: 13, 14 and 15 are derived directly from sequences listed at positions 152-161 and position 152-161* of Table 1. Furthermore, Table 4 lists SEQ ID NOS: 1, 2, 5, and 6 providing additional support for SEQ ID NOS: 16, 17 and 18. Table 4 also lists SEQ ID NOS: 3 and 4, which provide support for SEQ ID NOS: 13, 14 and 15. Applicants submit that these common motifs would be obvious to one of skill in the art upon review of the sequences listed in Tables 1 and 4. Furthermore, Applicants submit that the specification, in particular in Tables 1 and 4, provide sufficient description to

show one of skill in the art that the inventors had possession of the claimed invention at the time of the invention.

Further support for the consensus sequences of SEQ ID NOS: 13-18 may be found in the specification at page 25, line 24 to page 26, line 11. The importance of the KKK and QELD motifs shared by pSEB (150-161) and peptide p12 (150-161 and its derivatives) are highlighted. These motifs are spaced equally in both and may be important for antagonist activity, with the triple lysine motif conferring 3 positive charges.

Therefore, Applicants assert that the specification discloses sufficiently detailed, relevant characteristics which provide evidence that the Applicant was in possession of the claimed invention.

In addition, the Examiner has rejected claims 65-75 and 88-93 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in a way as to reasonably convey to one skilled in the art that the inventors, at the time of the invention, had possession of the claimed invention. The Examiner contends that the genus is highly variant and there is insufficient support for describing the genus. The Examiner also contends that SEQ ID NOS: 1-11 and 13-18 are insufficient to describe the genus and that the specification lacks the description of a function shared by the 10 amino acid fragments. In addition, the Examiner contends that one of skill in the art would conclude that the disclosure fails to provide a representative number of species to describe the genus.

Applicants respectfully disagree. SEQ ID NOS: 1-11 are clearly set forth in the specification and the consensus sequences derived therefrom (SEQ ID NOS: 13-18), as would be clearly apparent to one of skill in the art. Not only are there a sufficient number of representative species set forth in the specification, i.e. eleven, the specification also clearly

describes a shared function for the genus (specification, page 25, lines 24-27). This group of sequences, having KKK and QELD equally spaced apart, share toxin antagonist activity. One of skill in the art would view this disclosure as sufficient in presenting the number of representative species and the function shared by the members of the genus. It should be noted that claim 65-75, as well as claims 88-83, have been amended to recite peptides possessing the toxin antagonist activity shared by the ten amino acid fragment.

Claims 76, 90 and 93 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have corrected the typographical error of claim 76 in accordance with the Examiner's suggestions. In addition, claims 90 and 93 have been amended to replace "X" with "Xaa" to correct the inadvertent typographical error. Therefore, it will not be necessary to amend the claim to set forth any limitations of "X."

For the foregoing reasons, Applicants respectfully request the withdrawal of the rejections of claims 65-76 and 88-93.

The Rejections under 35 U.S.C. § 102 Should Be Withdrawn

Claims 50-65, 68, and 76-87 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tice et al. (US 5,407,609). The Examiner alleges that Tice et al. disclose formalinized staphyloccal enterotoxin (SEB) dissolved in 100µl deionized water. The Examiner also states that the toxoid disclosed by Tice et al. does not exhibit toxin agonist activity and allegedly having features homologous to the features recited in the instant claims, and therefore allegedly anticipates the presently claimed invention.

The present invention relates to certain isolated peptides, derived from pyrogenic exotoxins that induce toxic shock, including, but not limited to *Staphylococcus aureus* exotoxin B (SEB), that are capable of eliciting a protective immune response against toxic shock, as well as directly antagonizing toxin-mediated lymphocyte activation. In addition, these peptides do not exhibit toxin agonist activity. They are substantially homologous to or similar in amino acid sequence to a domain of such exotoxins that is not involved in binding of the toxin to the T-cell receptor (TCR) or to MHC Class II molecules, but has a specific structure, wherein the central turn in the toxin molecule starting within β- strand 7 and connecting it, via β- strand 8, to α-helix 4, and ending within α-helix 4. (See Fig. 2). In SEB, this domain encompasses amino acids 150-161 (SEQ. ID NO.: 12). Such isolated peptides directly inhibit pyrogenic toxin-mediated induction of IL-2, IFN-γ and/or TNF-β gene expression in normal peripheral blood mononuclear cells (PMBC).

In contrast to the present invention, the full length SEB protein taught by Tice et al. has been treated with formalin to produce a toxoid, which is then encapsulated. The toxoid is thus denatured and would not retain the conformation of the domain from which the peptides of the invention are derived, i.e. the central turn in the toxin molecule starting within β- strand 7 and connecting it, via β- strand 8, to α- helix 4, and ending within α-helix 4. Chemical modification of SEB would not only cause the full length protein to lose the specific structure as recited in claims 50, 76, 80, and 85, but also loss of activity due the loss of structure. The skilled artisan would readily appreciate that the antagonist activity of the synthetic peptides of the invention can be attributed to their ability to undergo induced fit to a critical target. A denatured protein loses the ability to undergo a shift in conformation, whereas the peptides of the invention, which are not denatured, are able to undergo induced fit and thus can compete with the toxin. In this

respect, the peptides of the invention mimic the native toxin, whereas the denatured protein disclosed in Tice et al. would not exhibit such activity. Therefore, Applicants submit that Tice et al. cannot anticipate claims 50-65, 68, and 76-87 of the present invention.

In addition, Tice et al. fails to disclose a peptide that is capable of antagonizing toxin-mediated T-lymphocyte activation, i.e. inhibition of SEB and other toxins, such as SEA, TSST-1 to mediate induction of IL-2, IFN-γ and/or TNF-β gene expression. Tice et al. does not test or present full-length or fragments of SEB as having the requirements of the presently claimed peptides. For this additional reason, Applicants submit that Tice et al. cannot anticipate claims 50-65, 68, and 76-87 of the present invention.

Claims 89-90 and 92-93 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ratti et al. The Examiner alleges that Ratti et al. discloses a protein encoded by ORF6D having sequences identical to those derived from *Chlamydia trachomatis*. The Examiner alleges that Ratti et al. discloses a peptide with the identical structural requirements set forth in the claims.

In contrast to the present invention, the peptide comprised within the protein disclosed in Ratti et al. fails to exhibit the capability of antagonizing toxin-mediated activation of T lymphocytes. In fact, Ratti et al. do not mention any sequence or peptide isolated that is capable of inhibiting SEB or other toxins, e.g. SEA and TSST-1, to mediate the activation of IL-2, IFN-γ and TNF-β. It should be emphasized that the peptides recited in claims 89, 90, 92 and 93 possess antagonist activity. Therefore, Applicants submit that Ratti et al. cannot anticipate claims 89-90 and 92-93 of the present invention.

In addition, claim 88 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Galinski et al. The Examiner alleges that Galinski et al. disclose a polymerase-associated

nucleocapsid phosphoroprotein obtained from parainfluenze virus, which meets the structural requirements set forth in claim 88.

For the reasons stated above, Applicants submit that Galinski et al. cannot anticipate the claims of the present invention. Galinski et al. fail to exhibit the capability of antagonizing toxin-mediated activation of T lymphocytes and do not mention any sequence or peptide isolated that is capable of inhibiting SEB or other toxins, e.g. SEA and TSST-1, to mediate the activation of IL-2, IFN-γ and TNF-β. Therefore, Galinksi et al. cannot anticipate claim 88.

Furthermore, claim 91 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Spriggs et al. The Examiner alleges that Spriggs et al. disclose a polymerase-associated nucleocapsid phosphoroprotein obtained from parainfluenza virus, which meets the structural requirements set forth in claim 91.

Similar to the cited art described above, the peptide of Spriggs et al. fails to exhibit the capability of antagonizing toxin-mediated activation of T lymphocytes. In addition, Spriggs et al. do not mention any sequence or peptide isolated is capable of inhibiting SEB or other toxins, e.g. SEA and TSST-1, to mediate the activation of IL-2, IFN-γ and TNF-β. Therefore, Applicants submit that Spriggs et al. cannot anticipate claim 91 of the present invention.

For the foregoing reasons, Applicants respectfully request the withdrawal of the rejection of the claims and reconsideration of the pending claims.

New claims

Applicants have added claims 94-99 to depend from claims 88-93 and recite that the peptides of claims 88-93 are capable of eliciting antibodies that block pyrogenic exotoxin-mediated activation of T-lymphocytes. Support for the new claims may be found in Example 7

of the specification at pages 43-45 and pages 50-51. Example 7 describes the generation of rabbit antiserum against the peptides of the present invention, which block the action of different pyrogenic exotoxins.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the outstanding rejections and allowance of the pending claims.

Applicants request a three month extension of time and enclose herewith the requisite fee as set forth in 37 C.F.R. § 1.17(a)(3). Applicants do not believe that any additional fee is required in connection with the submission of this document. However, should any fee be required, or if any overpayment has been made, the Commissioner is hereby authorized to charge any fees, or credit or any overpayments made, to Deposit Account 02-4377. A duplicate copy of this sheet is enclosed.

Respectfully submitted,
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